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RESEARCH PAPER

Edoardo Maragliano (1849-1940) and the immunogenicity of the tubercle bacillus: the pathway of a great italian physician

MARIANO MARTINI[1,2], NICCOLÒ RICCARDI[3], EDOARDO MARAGLIANO[4], FRANCESCO BRIGO[5]

[1] Department of Health Sciences, University of Genoa, Genoa, Italy; [2] Section Chief of "Liguria-StopTB Italia Onlus", Genoa-Milan, Italy; [3] Department of Infectious - Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Verona, Italy; [4] Indipendent Scholar, Genoa, Italy; [5] Department of Neurology, Hospital of Merano (SABES-ASDAA), Italy

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Summary

Edoardo Maragliano (1849-1940) was an Italian physician; he played a central role in medicine's "renaissance" in Italy and Europe. After beginning his academic career as a professor of pathology, he became full professor of internal medicine in 1881. While he studied all fields of internal medicine, his research focused mainly on tuberculosis. Thanks to his experiments in the medical clinic, Maragliano announced the possibility of immunization against Mycobacterium tuberculosis. Although criticized for using an inactivated vaccine, Maragliano continued to advocate vaccination with any type of vaccine.

Maragliano keenly contributed to the still ongoing process of understanding the difficult interaction between Mycobacterium tuberculosis and the infected host.

Edoardo Maragliano (1849-1940) was born in Genoa on 1 June 1849 into a family of Ligurian origin. Having studied classics, first at the "Ginnasio" of the Padri Scolopi and then at high school, he matriculated at the Faculty of Medicine of the University of Genoa. After his first years of study, he moved to Naples, where he completed his course in medicine, graduating with full marks in 1870.

In Naples, he was initially a pupil of Prof. Salvatore Tommasi (1813-1888) and Prof. Arnaldo Cantani (1837-1893). Subsequently, on returning to Genoa, he became an assistant to Errico de Rienzi (1839-1921), the director of the Medical Clinic, and in 1877 was appointed to teach General Pathology, which he did until 1881 [1]. Indeed, in that year, he was appointed Ordinary Professor of Clinical Medicine in Genoa, a position he held until 1924. During his tenure, his department became a significant point of reference in medical field. Maragliano was an indefatigable scholar and a prolific author, publishing 2453 scientific works of notable importance. Among his main publications, his "*Trattato delle malattie dei polmoni*" (Treatise on lung diseases) and his original monographs on nephritis, fever and blood are worth mentioning.

In the present article, we will discuss his contribution to the study of tuberculosis (TB) and the immunity elicited by infection with Mycobacterium tuberculosis and by anti-tuberculosis vaccination.

From 1890 onwards, Maragliano devoted much of his research to studying immunity towards tuberculosis infection. As an astute pioneer in this field, in 1900 he founded an innovative institute for the study of tuberculosis and infectious diseases: the Maragliano Institute in Genoa (Italy). At the end of the 19th century, the existence of immunity to tuberculosis was not yet recognized; it was claimed that TB was an infection" sui generis", different from others, and the notion that a state of immunity could be elicited in humans was rejected. Maragliano was the first to cast doubt on this idea and demonstrated that it was indeed possible to immunize people against TB, just like any other infectious disease. In order to fully understand Edoardo Maragliano's work, we need to go back to the period immediately following the discovery of the TB bacillus by Robert Koch (1843-1910) [2].

In 1882, although immunology was only in its infancy, it was already known that any substance introduced into a biological system displayed antigenicity (immunogenicity), that is to say, the antigen induced the production of antibodies, which then mounted an immune response. Erroneously, however, it was believed that antigenicity was a property intrinsic to any substance, such as its molecular weight or its absorption spectrum, for example. Based on these assumptions, many researchers believed that they could obtain a protective immune response by inoculating bacterial matter into an animal, without taking into account its quantity, and the conditions and mode of inoculation. These researchers, however, saw their hopes dashed, so much so that and as a consequence of their, owing to the failure in demonstrating the immunogenicity of the TB bacillus, they concluded that it would never be possible to create a vaccine against TB [3].

This was the state of research between 1884 and the

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early 1890s. By then, Maragliano had been running the Medical Clinic in Genoa for a decade where he promoted the study and understanding the immunogenicity of Mycobacterium tuberculosis". Nevertheless, his stance was not that of the pure bacteriologist, but rather that of the physician who remained focused on the patient [4].

Maragliano needed to demonstrate the antigenicity of the TB bacillus experimentally in an animal model. To prove the immunogenicity of the bacillus, Maragliano adopted the following stratagems:

1. Firstly, it was necessary to calibrate the intensity of the bacterial load very carefully; i.e., the right amount had to be inoculated: neither too much nor too little. In order to trigger a defensive movement, Maragliano claimed that the "offended cells" had to react. If, however, the "*offense*" were too strong, the ability to react would be weakened and eventually arrested;
2. Secondly, the gradual appearance of antibodies and the disappearance of the bacilli had to be monitored, in order to determine when the immune response had reached its peak (maximum development). According to Maragliano, this should generally occur around the 90th day after inoculation;
3. Thirdly, only after respecting this timing could the animal be tested to determine whether it was capable of *"defending itself"*; i.e., of reacting to a new bacterial load that was equal to the smallest load that would be able to kill a control animal. In Maragliano's view, this last precaution was not only indespensable for the experiment to be successful; it also explained why the tests conducted without these stratagems had failed [5].

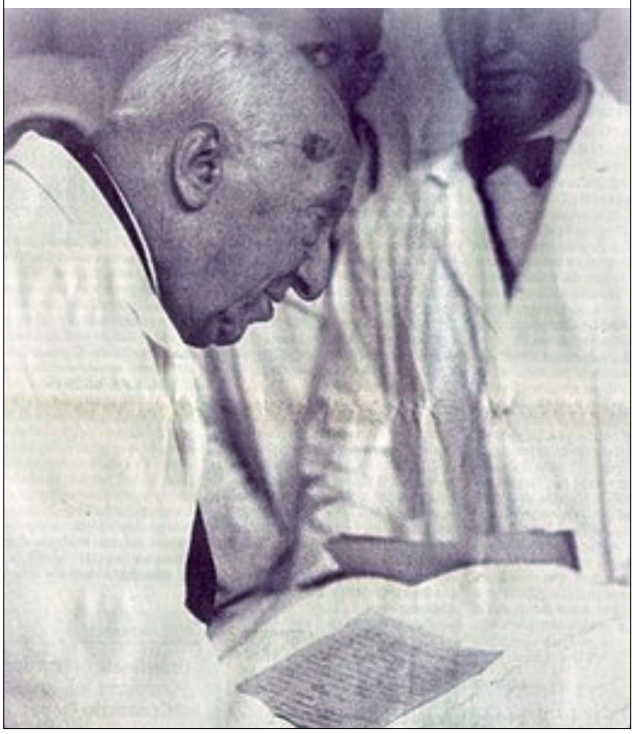
The stratagems implemented by Maragliano led to the development of anti-tuberculosis vaccination: not only that of the Professor himself, the *"Vaccino Maragliano"*, but also of all those that were to follow [6].

Indeed, Maragliano's greatest merit probably lies in the fact that he was the first to introduce what he himself called *"stratagems"*; this was confirmed in his farewell lesson on 28 June 1924 (7) after 43 years of teaching, in which he clearly stated:

"Here, on this solemn occasion, it behooves me to make a declaration. The therapeutic applications of our studies and the specific therapy that has sprung from those studies are of secondary importance. Indeed, what constitutes the chief boast of our School is the discovery of a series of stratagems which demonstrated the existence of an immunogenicity of the bacillus that was functionally dependent on the biological system and the conditions used".

These "stratagems" worked out by Maragliano concerning *Mycobacterium tuberculosis* must, still today, be borne in mind in the case of any other antigen. Indeed, in every immunology textbook, we always find the concept that the formation of antibodies does not depend only on the inoculation of the antigen into a suitable animal, but also on other conditions, such as, for example, the quantity and quality of the antigen injected, the route of inoculation, the immune status of the subject, and the frequency of the various follow-up tests.

Fig. 1. Prof. Edoardo Maragliano (1849-1940) (Wikipedia Commons).



Indeed, the principal merit of the school directed by Prof. Edoardo Maragliano, as he himself pointed out in his farewell lesson, was *"… having discovered a series of facts that demonstrated the existence of a tubercular immunity, which had hitherto been denied, and having laid the foundations of the new conceptions of the pathology of tubercular diseases, conceptions which are now all based on immunity"* (6).

As the great scientist Saturnin Arloing (1846-1911) publicly stated in 1906 in Genoa, in a speech on Maragliano's studies: *"Until 1895, we despaired of being able to obtain tubercular immunity. Through his discoveries, Maragliano raised the spirits of researchers from the depths of despondency into which they had fallen. At first, the announcement was greeted with reservation, but then confirmation came from all sides: what he had said was true. This was the first word of "serene justice" that our school received from the scientific community, and it emanated from a scientist of international eminence"*[8].

Maragliano actively contributed to the still ongoing process of understanding the difficult interaction between *Mycobacterium tuberculosis* and the host [9,10].

Even today we must always observe and emphasize that infection prevention and control measures are particularly important in public health facilities because there is a risk of transmission of the tuberculosis bacterium "Mycobacterium tuberculosis"; the World Health Organization (WHO) developed recommendations according to the methods defined in the WHO handbook for guideline development [11].

Moreover, we should always consider and reflect on one

of the most important aspects in this long pathway: a real and successful vaccine.
We still have to remember today that only a really efficacious vaccine will enable us to eradicate TB.
According to the World Health Organization, tuberculosis (TB) is the leading cause of death from infectious disease worldwide (WHO, 2017). While there is no effective vaccine against adult pulmonary TB, more than a dozen vaccine candidates are in the clinical trial pipeline [12]. But how long will we still have to wait?

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MM and EM designed the study. MM and EM conceived the study; MM and EM drafted the manuscript; MM, NR and FB revised the manuscript. MM, FB performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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Correspondence: Mariano Martini, Department of Health Sciences, University of Genoa, Genoa, Italy – E: mail: mariano.yy@gmail.com

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